International Journal of Antimicrobial Agents 53 (2019) 225–233

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Review

Cefazolin vs. anti-staphylococcal penicillins for treatment of methicillin-susceptible *Staphylococcus aureus* bloodstream infections in acutely ill adult patients: Results of a systematic review and meta-analysis ☆

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ARTICLE INFO

Article history:
Received 13 June 2018
Accepted 17 November 2018

Editor: Jason Roberts

Keywords:
Methicillin-susceptible *Staphylococcus aureus*
Bloodstream infection
Anti-staphylococcal penicillin
Cefazolin
Antibiotic stewardship

ABSTRACT

A systematic literature review and meta-analysis was conducted to evaluate the comparative efficacy and tolerability of cefazolin vs. anti-staphylococcal penicillins (ASPs) for methicillin-susceptible *Staphylococcus aureus* (MSSA) bloodstream infections (BSI). Utilizing published regression models, included studies were stratified into subgroups of high and low pre-probability of mortality. Cefazolin was associated with significantly lower rates of treatment failure (odds ratio [OR]: 0.70; 95% confidence interval [CI]: 0.61-0.82; $P<0.001$; $I^2=14\%$) and crude, all-cause mortality (OR: 0.69; 95% CI: 0.59-0.81; $P<0.001$; $I^2=18\%$) compared with ASP therapy. Overall risk of treatment-related adverse drug reactions was numerically lower with cefazolin (OR: 0.39; 95% CI: 0.15-1.00; $P=0.05$). Subgroup sensitivity analyses of studies conducted in less severely ill patients were similar to the combined analysis. The role of cefazolin in the most severely ill patients with MSSA BSI should be prospectively evaluated.
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1. Introduction

Staphylococcus aureus (SA) bloodstream infections (BSI) continue to be a leading cause of morbidity and mortality within healthcare systems, particularly the intensive care unit (ICU) [1–3]. Extensive use of intravascular catheters in critically ill patients is a major risk factor in acquisition of ICU-BSI, with SA representing one of the most commonly isolated organisms in ICU-BSI [3–7]. Prompt initiation of effective antimicrobial therapy is essential to reduce the risk of mortality in BSI, particularly in patients with sepsis and septic shock [8–10]. Timely optimization of antibiotics as part of a comprehensive, multidisciplinary approach has also been advocated to reduce antimicrobial resistance, treatment-related adverse drug reactions (ADRs), and overall hospital costs [11–13].

Traditionally, anti-staphylococcal penicillins (ASPs), such as nafcillin or oxacillin, have been regarded as first-line in the treatment of serious methicillin-susceptible *Staphylococcus aureus* (MSSA) BSI. The pharmacokinetics of beta-lactams are often complex and unpredictable in the ICU setting, and the emergence of drug-related adverse events disproportionately affects this population [14,15]. Cefazolin is associated with greater dosing convenience, a longer half-life, and fewer ADRs compared with nafcillin or oxacillin. However, concerns about the risk of treatment failure with cefazolin and inactivation by type A beta-lactamases in the setting of high-burden infections have relegated it to alternative status

☆ Portions of this paper were presented as a poster at IDWeek, 3 to 7 October 2018; San Francisco, CA.

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https://doi.org/10.1016/j.ijantimicag.2018.11.013
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[16,17]. Recent studies of MSSA BSI indicate that infection outcomes are similar between patients treated with cefazolin or ASPs [18–25]. Individual studies have been constrained by sample size, event rate, and severity of illness. We reviewed the literature to compare the effectiveness and tolerability of cefazolin to ASP therapy for the treatment of MSSA BSI stratified by study-level severity of illness.

2. Materials and methods

2.1. Systematic literature review and study selection

A systematic search of the literature was performed using the PubMed, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Review (CDSR) electronic databases from inception until 28 July 2017. Details of the systematic review and study inclusion are provided in the Supplemental Material. Briefly, a comprehensive, full-text search, including root words and derivatives, was applied using the following terms: (*Staphylococcus aureus*) AND (methicillin susceptible OR methicillin sensitive OR meticillin susceptible OR meticillin sensitive OR MSSA) AND (cefazolin) AND (bloodstream OR bacteremia OR bacteraemia). Studies retrieved using the search strategy were first screened based on their titles and abstracts by two independent reviewers (JC and KA) for any articles written in English and reporting treatment outcomes for SA bacteremia. These articles were then evaluated for eligibility based on pre-established inclusion criteria and were then cross-checked by a third reviewer (BL) (see Supplemental Material). References of included studies and review articles or other studies known to the reviewers were also screened. Eligible studies were reviewed in full and entered into Review Manager (RevMan) v.5.3 [26].

2.2. Data extraction, definitions, and study outcomes

Data elements of interest included treatment failure, crude (i.e., unadjusted) study-defined mortality, and treatment-associated ADR counts. We also extracted primary study characteristics (e.g., first author, publication year, study design, and sample size), demographic variables (e.g., age, sex, and severity of illness measures), and infection characteristics (e.g., metastatic, high-burden, or high-inoculum classification). High-burden infections were defined as MSSA bacteremia with concomitant endocarditis, osteomyelitis, deep-tissue infections or abscesses, vascular grafts, pneumonia, meningitis, or as identified by the investigators. Infections classified by investigators as 'high-inoculum' were also considered high-burden infections. ASP therapy was defined as usage of intravenous oxacillin, nafcillin, or cloxacillin. Corresponding authors were contacted when data elements were missing or clarification was necessary.

Average study-level severity of illness scores were re-expressed as average mortality probabilities using published regressions [e.g., probability = elogit / (1+elogit); **Table S2**] [27–33]. A detailed summary can be found in the Supplementary Material. Study-level risk of bias was assessed by two investigators (SKW and NJR) with discrepancies resolved by a third (BJL). Risk of bias among prospective studies was assessed using the Cochrane Risk of Bias Assessment Tool [34], and risk of bias among retrospective studies was assessed using the Newcastle-Ottawa Scale (NOS) [35]. The risk of publication bias for each outcome was assessed by visual inspection of funnel plots and Egger's test for funnel plot asymmetry. If asymmetry was detected, a trim and fill analysis was conducted [36].

Treatment failure was defined as the composite of persistence of BSI, MSSA recurrence, non-resolution of infection, or all-cause mortality defined at the study level. ADRs were defined as renal, hepatic, dermatological, or systemic reactions consistent with known adverse reactions as documented in the approved product labelling [37–39]. ADRs were classified as treatment-associated if they occurred during active receipt of cefazolin or ASP therapy.

The primary outcome of this review was treatment failure among patients receiving cefazolin vs. ASPs for MSSA BSI. Secondary outcomes included crude, all-cause mortality (defined according to the individual methods of each study) and treatment-associated ADRs. Binary outcomes from each study were extracted as counts, and continuous outcomes were extracted as means or medians with variance estimated from standard deviations, interquartile ranges, or ranges [34,40].

2.3. Statistical analysis

Pooled odds ratios (ORs) with 95% confidence intervals (CI) were calculated for all outcomes. Statistical heterogeneity between studies was assessed using the chi-square test ($P<0.10$) of heterogeneity and the I^2 measure ($P>50\%$) of inconsistency. When low statistical heterogeneity was observed or when the outcome measure was associated with low measurement bias, the Mantel-Haenszel fixed-effects model was used; otherwise, the random-effects model was utilized. Univariate meta-regression analyses were performed to evaluate potential modifiers of effect-size, including metastatic infections, high-burden infections, and high average study severity of illness, when available. Meta-analyses were performed using RevMan v.5.3 [26]. Meta-regressions and funnel-plot asymmetry tests were conducted using the "metafor" package (version 2.0-0) [41] for the R environment (version 3.4.3) [42]. Meta-analyses were conducted to obtain pooled effect size estimates across all studies, and a planned subset analysis was conducted to evaluate the impact of high vs. low study-level average mortality probability as a global measure of comorbidity within each study. The stratification between high and low average mortality probabilities was set at 15% (i.e., the 25th percentile of observed mortality rates in previous SA bacteremia studies) to sensitively classify severely ill patients [43].

3. Results

3.1. Literature search results

The systematic review is summarized in Fig. 1. A search of the PubMed, Web of Science, CENTRAL, and CDSR electronic databases identified 866 indexed abstracts, of which 762 were excluded as they were duplicates (n = 38), written in a language other than English (n = 122), or reporting data for non-SA bacteremia (n = 602), resulting in 104 full-text articles that were assessed for eligibility. Nine systematically identified studies were included in meta-analysis [18–25,44].

Reasons for exclusion were: reporting of microbiological or animal model data (n = 16), epidemiological studies and those identifying predictors for clinical outcomes (n = 10), inappropriate study design as case reports/series (n = 6) or review articles and commentaries (n = 19), treatment assessment in resistant strains of SA (n = 5), evaluation of non-cefazolin vs. ASP comparisons (e.g., vancomycin, gentamicin) (n = 13), and impact of infectious diseases consultation (n = 7), echocardiogram (n = 10), penicillin allergy reporting (n = 3), and treatment duration (n = 2) on BSI outcomes. Four articles evaluated the efficacy of several beta-lactams in SA bloodstream infections but no comparative data for cefazolin and ASPs were reported.

The corresponding authors of six articles were contacted for provision of additional information, of which four replied with the requested data [18,23–25]. Two studies evaluated patients within

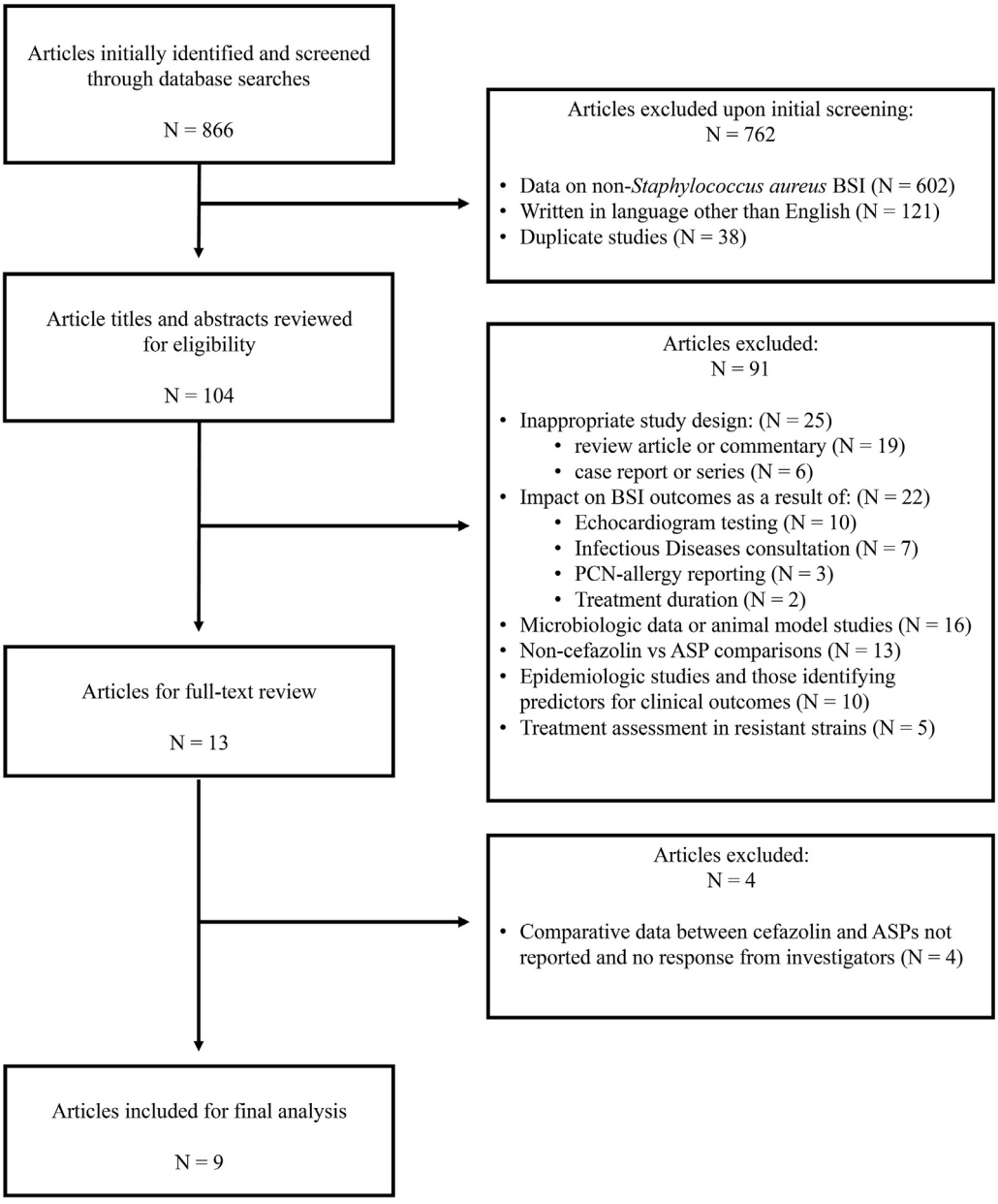

Fig. 1. PRISMA flow diagram for study inclusion.
Figure legend: ASPs, anti-staphylococcal penicillins; BSI, bloodstream infection; PCN, penicillin.

close geographical and temporal proximity [21,44]. In a multicenter study, 161 patients were evaluated, and a single-center pre-post quasi-experimental study included 43 additional patients who were not included in the original study [21,44]. As a de-duplication procedure, the subset of patients not included in S. Rao et al. 2015 were classified as belonging to B. Lee et al. 2017 [21,44].

3.2. Characteristics of included studies and patient demographics

The study characteristics of included papers are outlined in Table 1. The majority of studies were retrospective in nature with only one prospective cohort study included [23]. Four studies were multicenter [19,20,23–25], with the number of study sites ranging from 2 to 122. No prospective randomized controlled trials were identified. Overall, six studies reported unadjusted 90-day mortality [18–20,22,23,25]; 30-day mortality [24] and end-of-study mortality [21,44] were reported in the remaining three studies. Four studies employed propensity score matching, though raw data were available from these studies either through direct data extraction or individual investigator contact [18,20,22,23].

Of the 4442 included patients, 1726 (38.9%) received cefazolin and 2716 (61.1%) received an ASP (105 oxacillin, 358 nafcillin, and 249 dicloxacillin). In one study, both oxacillin and nafcillin were combined as a single ASP group, which accounted for 2004 patients [25]. High-burden infections were reported in 30.5% (n = 1357) of all patients, with the most common source being bone and joint infections (48.3%), followed by endocarditis (27.5%), abscess (9.9%), or pneumonia (9.1%). The frequency of epidural or intraspinal abscess was 6.8% (n = 92/1357) overall. Patients were predominantly male (86.6%) with a mean [SD] age of 57.4 [14.2] years, which did not differ between cefazolin (82.9% male; mean age 58.8 [14.5] years) or ASP (89.0% male; mean age 56.0 [14.0] years) treatment groups.

Infection dissemination and severity of illness differences between cefazolin and ASP-treated patients are also summarized in Table 1. Metastatic MSSA infection was reported in five

Table 1
Characteristics of selected studies[a]

Author; year [ref]	Study design; time period, country	No. of patients; treatment groups	Mean age [SD] years; male n (%); severity of illness median [IQR]	High burden infections[b]			Efficacy outcomes		Safety
				Source of high-burden infections	High-burden infections	Metastatic MSSA infection	Treatment failure	Mortality rates	Adverse drug reactions
Lee S, et al., 2011 [18]	Retrospective, PS-matched, case-controlled, single center; 2004-2006, Korea	n = 133; CEF (n = 49) NAF (n = 84)	CEF: 55 [20]; male 29 (59) NAF: 52 [17]; male 49 (58)	CEF: BNJ 10 (20.4); ENDO 1 (2); PNA 4 (8); MISC 5 (10.2) NAF: BNJ 11 (13.1); ENDO 13 (15.5); PNA 11 (13.1); MISC 9 (10.7)	CEF: 20 (41.0) NAF: 44 (52.0)	CEF: 8 (16) NAF: 23 (27)	CEF: 7 (14) NAF: 14 (16)	CEF [e]: 7 (14) NAF [e]: 14 (16)	NR
Li J, et al., 2014 [19]	Retrospective, multicenter (n = 2), cohort; 2008-2012, USA	n = 93; CEF (n = 59) OXA (n = 34)	CEF: 51 [10]; male 44 (74.6); PITT 0 [0-1] OXA: 51 [14]; male 28 (82.4); PITT 0 [0-1]	CEF: BNJ 18 (31); ENDO 15 (25); PNA 2 (4) OXA: BNJ 20 (59); ENDO 4 (12); PNA 2 (6)	CEF: 35 (59.3) OXA: 26 (76.5)	CEF: 20 (33.9) OXA: 12 (35.3)	CEF: 14 (23.7) OXA: 16 (47.1)	CEF [e]: 0 (0) NAF [e]: 1 (2.9)	CEF: 2 (3.4) OXA: 10 (29.4)
Bai A, et al., 2015 [20]	Retrospective, multicenter (n = 6), cohort; 2007-2010, Canada	n = 345; CEF (n = 105) CLX (n = 249)	CEF: 68 [18.8]; male 58 (55.2) CLX: 65.7 [19.4]; male 166 (66.7)	CEF: ABS 2 (2); BNJ 15 (14); PNA 17 (16); ENDO 2 (2); MISC[d] 7 (7) CLX: ABS 19 (8); BNJ 28 (11); PNA 44 (18); ENDO 30 (12); MISC[d] 35 (14)	CEF: 43 (41) CLX: 156 (62.7)	NR	CEF: 27 (25.7) CLX: 79 (31.7)	CEF [e]: 21(20) CLX [e]: 75 (30.1)	NR
Rao S, et al., 2015 [21]	Retrospective, multicenter (n = 2), cohort; 2010-2013, USA	n = 161; CEF (n = 103) OXA (n = 58)	CEF: 53.3 [16.7]; male 60 (58.3); APACHE-II 13 (6.3) OXA: 53.6 [18.4]; male 36 (62.1); APACHE-II 10.3 (5.8)	CEF: ABS 6 (5.8); BNJ 9 (8.7); ENDO 17 (16.5) OXA: BNJ 7 (12.1); CNS 1 (1.7); ENDO 12 (20.7)	CEF: 32 (31.1) OXA: 20 (34.5)	CEF: 30 (29.1) OXA: 11 (19.0)	CEF: 6 (5.8) OXA: 7 (12.1)	CEF [f]: 1 (1.0) OXA [f]: 3 (5.2)	CEF: 8 (7.8)OXA: 2 (3.5)
Pollett S, et al., 2016 [22]	Retrospective, single center, cohort; 2008-2013, USA	n = 100; CEF (n = 70) NAF (n = 30)	CEF: 53 [15.1]; male 22 (31.4); CCI 4 [2–7] NAF: 50.4 [12.5]; male 7 (23.3); CCI 3 [1–7]	CEF: ABS 5 (7.1); BNJ 5 (7.1); PNA 1 (1.4); ENDO 10 (14.2); PROS 5 (7.1) NAF: ABS 2 (6.7); BNJ 3 (10.0); PNA 4 (13.3); ENDO 5 (16.7); PROS 1 (3.3)	CEF: 26 (37.1) NAF: 15 (50.0)	NR	CEF: 5 (7.1) NAF: 5 (16.7)	CEF [e]: 5 (7.1) NAF [e]: 5 (16.7)	NR

(*continued on next page*)

Table 1 (*continued*)

Author; year [ref]	Study design; time period, country	No. of patients; treatment groups	Mean age [SD] years; male n (%); severity of illness median [IQR]	High burden infections[b]			Efficacy outcomes		Safety
				Source of high-burden infections	High-burden infections	Metastatic MSSA infection	Treatment failure	Mortality rates	Adverse drug reactions
Lee B, et al., 2017 [44]	Retrospective, single center, quasi-experimental, cohort; 2010-2014, USA	n = 43; CEF (n = 30) OXA (n = 13)	CEF: 60.5 [19.3]; male 13 (43.3); APACHE-II 14.2 [4.8] OXA: 49.5 [13]; male 4 (30.8); APACHE-II 11.9 [5.4]	CEF: ABS 6 (20); BNJ 1 (3.3); PNA 3 (10); ENDO 4 (13.3) OXA: ABS 3 (23.1); BNJ 2 (15.4); PNA 1 (7.7); ENDO 2 (15.4)	CEF: 14 (46.7) OXA: 8 (61.5)	CEF: 5 (16.7) OXA: 5 (38.5)	CEF: 1 (3.3) OXA: 0 (0)	CEF [f]: 0 (0) OXA [f]: 0 (0)	CEF:1 (5.1)OXA:0 (0)
Flynt L, et al., 2017 [24]	Retrospective, multicenter (n = 4), cohort; 2013-2015, USA	n = 149; CEF (n = 68) NAF (n = 81)	CEF: 65.4 [15]; male 23 (33.8); PITT ≥ 4: 7 (9.4) NAF: 54.8 [16]; male 47 (58); PITT ≥ 4: 13 (15.9)	CEF: BNJ 13 (19.1); ENDO 11 (16.2); PNA 9 (13.2) NAF: BNJ 20 (24.7); ENDO 22 (27.2); PNA 7 (8.6)	CEF: 33 (48.5) NAF: 49 (60.5)	NR	CEF: 12 (17.6) NAF: 11 (13.6)	CEF [g]: 4 (6.0) NAF [g]: 4 (5.0)	CEF:5 (7.4)NAF:19 (23.5)
McDanel J, et al., 2017 [25]	Retrospective, multicenter (n = 122), cohort; 2003-2010, USA	n = 3167; CEF (n = 1163) ASP (n = 2004)	CEF: 64 [NR]; male 1133 (97.4); APACHE-III 34 [NR] ASP [c]: 64 [NR]; male 1974 (98.5); APACHE-III 33 [NR]	CEF: BNJ 138 (11.9); ENDO 52 (4.5); ISP ABS 27 (2.3) ASP: BNJ 267 (13.3); ENDO 145 (7.2); ISP ABS 65 (3.2)	CEF: 217 (18.7) ASP: 477 (23.8)	NR	CEF: 231 (19.8) ASP: 502 (25.0)	CEF [e]: 231 (19.8) ASP [e]: 502 (25.0)	NR
Lee S, et al., 2017 [23]	Prospective, multicenter (n = 10), cohort; 2013-2015, Korea	n = 242; CEF (n = 79) NAF (n = 163)	CEF: 59 [15.5]; male 48 (60.8); SOFA 2.1 (2.5) NAF: 62.7 [15.7]; male 106 (65); SOFA 3.7 (3.2)	CEF: BNJ 28 (35.4); PNA 3 (3.8); ENDO 4 (5.1); IAI 2 (2.5) NAF: BNJ 61 (37.4); PNA 16 (9.8); ENDO 24 (14.7); IAI 3 (1.8); CNS 1 (0.6)	CEF: 37 (46.8) NAF: 105 (64.4)	CEF: 10 (12.7) NAF: 23 (14.1)	CEF: 24 (30.4) NAF: 82 (50.3)	CEF [e]: 2 (2.5) NAF [e]: 24 (14.7)	CEF: 10 (12.7)NAF: 48 (29.4)

Abbreviations: ABS, abscess; ADR, adverse drug reaction; APACHE, Acute Physiology and Chronic Health Evaluation; ASP, anti-staphylococcal penicillin; BNJ, bone/joint and osteomyelitis; CCI, Charlson Comorbidity Index; CEF, cefazolin; CLX, cloxacillin; CNS, central nervous system; ENDO, endocarditis; IAI, intra-abdominal infection; IQR, interquartile range; ISP, intraspinal; MSSA, methicillin-susceptible *Staphylococcus aureus*; NAF, nafcillin; NR, not reported; OXA, oxacillin; PITT, PITT bacteremia score; PNA, pneumonia; PROS, prosthetic device; PS, propensity-scored; SD, standard deviation; SOFA, sequential organ failure score.

[a] Values are reported as *n* (%) unless indicated otherwise.

[b] High-burden infections defined as MSSA bacteremia accompanied by endocarditis, unremoved vascular graft infection, osteomyelitis, pneumonia, deep-seated abscess, and/or metastatic infection or as identified by the investigators.

[c] Corresponding to nafcillin or oxacillin therapy.

[d] Reported as other sources including intra-abdominal, biliary tract, CNS, endovascular, mycotic aneurysm, or cardiac device associated.

[e] 90-day, all-cause mortality.

[f] End of study, all-cause mortality.

[g] 30-day, all-cause mortality.

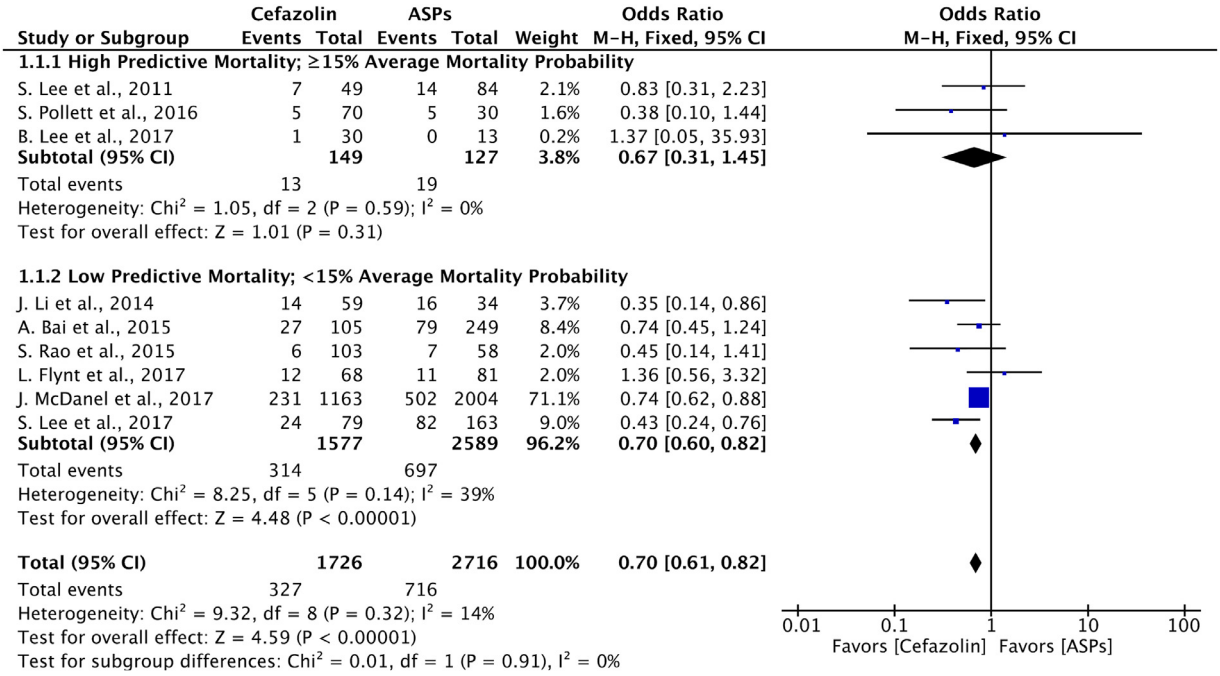

Fig. 2. Forest plot for composite treatment failure according to high vs. low study-level mortality probability.
Figure legend: ASP: anti-staphylococcal penicillins.

[18,19,21,23,44] of the included studies. The frequency of disseminated infection was similar between cefazolin and ASP-treated patients (22.8% vs. 21.0%; $P=0.56$). Average study-level mortality probabilities were similar between the cefazolin and ASP treatment groups (15.6% vs. 15.1%). The frequency of study-level mortality probabilities ≥15% was more common in the cefazolin-treated group (50% vs. 25%).

3.3. Treatment failure

Therapeutic efficacy was evaluated in all 9 studies: treatment failure was reported in 18.9% (n = 327) of cefazolin-treated patients and 26.4% (n = 716) of ASP-treated patients. The meta-analyses for treatment failure are graphically displayed in Fig. 2. Study heterogeneity was low ($P=0.32$; $I^2=14\%$). There was a significant reduction in treatment failure with cefazolin compared with ASPs (OR: 0.70; 95% CI: 0.61-0.82; $P<0.001$). Within the subset of studies demonstrating average mortality probabilities <15% (n = 6), cefazolin therapy remained protective against failure (OR: 0.70; 95% CI: 0.60-0.82; $P<0.001$; $I^2=39\%$). In the subset of studies with average mortality probabilities ≥15% (n = 3), point estimates supported a reduced odds of failure with cefazolin but were not significant (OR: 0.67; 95% CI: 0.31-1.45; $P=0.31$; $I^2=0\%$) (Fig. 2). Univariate meta-regression analyses failed to identify a significant effect of metastatic (5 studies; $P=0.89$) or high-burden MSSA infection rates (9 studies; $P=0.23$) on the risk of treatment failure.

3.4. Mortality

Overall, the observed all-cause mortality rates were 15.7% (n = 271) in the cefazolin group and 23.1% (n = 628) in the ASP group. The meta-analyses for mortality are graphically displayed in Fig. 3. Study heterogeneity was low ($P=0.29$; $I^2=18\%$). Significantly lower odds of all-cause mortality were evident among patients treated with cefazolin vs. ASPs (OR: 0.69; 95% CI: 0.59-0.81; $P<0.001$). Receipt of cefazolin therapy was protective against mortality in the subset of studies (n = 6) with average mortality probabilities <15% (OR: 0.70; 95% CI: 0.59-0.82; $P<0.001$; $I^2=35\%$). In the subset of studies with average mortality probabilities ≥15% (n = 3), the effect size estimates again supported a reduced odds of mortality with cefazolin but were not significant (OR: 0.64; 95% CI: 0.29-1.43; $P=0.28$; $I^2=0\%$) (Fig. 3). Improved mortality with cefazolin was also observed within the subset of studies reporting 90-day mortality (n = 7; OR: 0.69; 95% CI: 0.59-0.82; $P<0.001$; $I^2=25\%$) (**Figure S1**). Univariate meta-regression analyses failed to identify a significant effect of metastatic (5 studies; $P=0.35$) or high-burden MSSA infection rates (9 studies; $P=0.17$) on mortality risk.

3.5. Adverse drug reactions

Among 688 patients from 5 included studies, 15.3% (n = 105) of patients experienced treatment-associated ADRs [19,21,23,24,44]. The meta-analysis for ADRs is graphically displayed in Fig. 4. Study heterogeneity was high ($P=0.05$; $I^2=59\%$), and a random-effects model was utilized. The incidence of ADRs with cefazolin ranged from 3.3% to 12.7% while those with ASPs occurred between 3.5% and 29.5%. Treatment-associated ADRs were reported in 7.7% of cefazolin patients and 22.6% of ASP patients. Overall, the risk of ADRs was numerically lower with cefazolin treatment in a pooled analysis (OR: 0.39; 95% CI: 0.15-1.00; $P=0.05$).

3.6. Risk of bias

The potential impact of publication bias for treatment failure and all-cause mortality was assessed and graphically displayed in **Figure S2**. A funnel plot of the 9 included studies did not identify significant publication bias with respect to treatment failure (Egger's test $P=0.37$). However, visual inspection of the funnel plot for mortality indicated potential left-sided skewness (Egger's test $P=0.07$). In a trim and fill analysis (Egger's test $P=0.79$), treatment with cefazolin therapy remained significantly protective

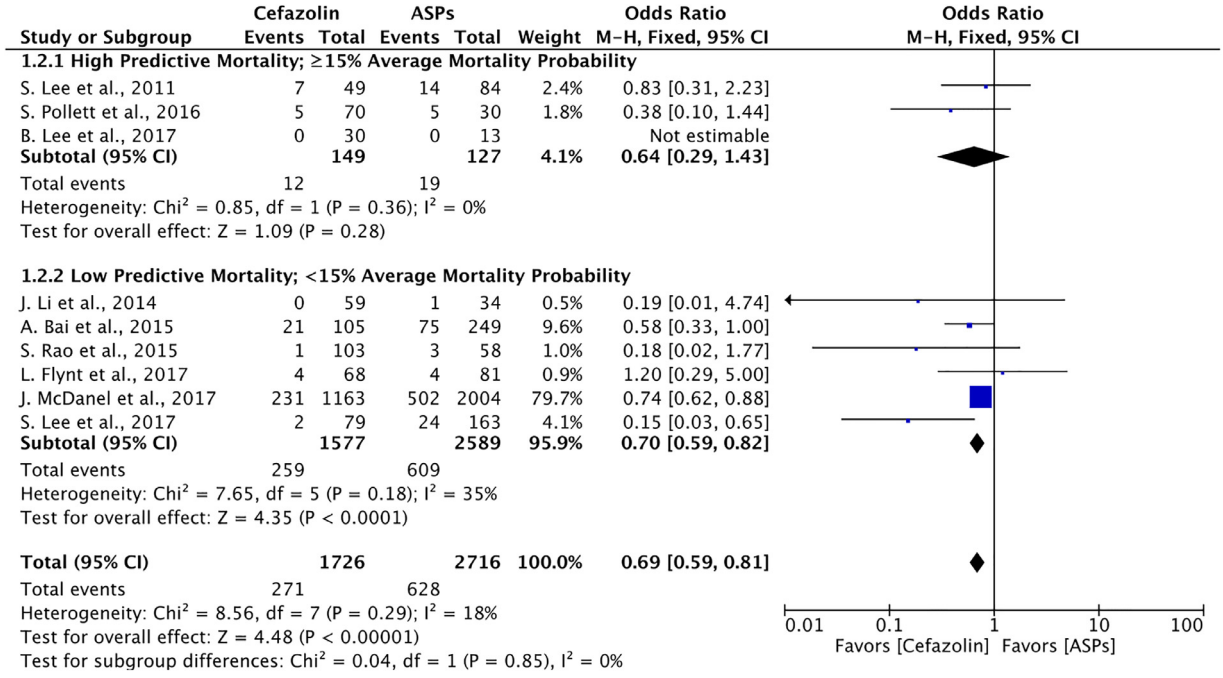

Fig. 3. Forest plot for end of study all-cause mortality according to high vs. low study-level mortality probability.
Figure legend: ASP: anti-staphylococcal penicillins.

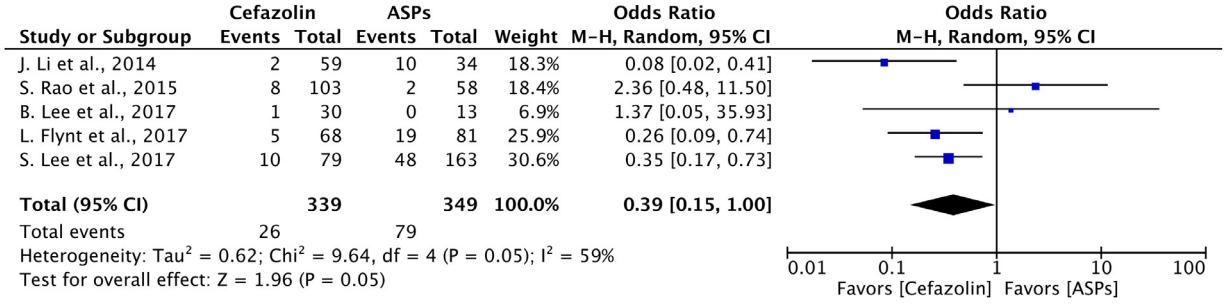

Fig. 4. Forest plot for treatment-associated ADRs in patients receiving cefazolin vs. ASPs.
Figure legend: ADRs, adverse drug reactions; ASP: anti-staphylococcal penicillins.

against mortality (OR: 0.66; 95% CI: 0.51-0.85; $P<0.001$). No funnel plot asymmetry was detected with treatment-associated ADRs ($P=0.06$). The risk of bias for non-randomized studies is summarized in **Table S3**. Overall, the risk of bias assessment concordance was 95% across all studies. Only one prospective study was identified, for which high risk of bias was exhibited in two of seven categories. Of the 8 retrospective studies, 7 were determined to meet 7 to 9 stars out of 9 on the NOS scoring tool, and one study was determined to meet 5 or 6 of 9 stars. None of the included studies scored less than 6 stars. The most frequently marked down criterion among the retrospective studies was inadequacy or lack of follow-up (75%; n = 6/8), a common finding among retrospective studies.

4. Discussion

We systematically evaluated and summarized the findings of contemporary studies comparing clinical outcomes of patients with MSSA BSI receiving cefazolin or ASPs as definitive therapy. We found that cefazolin was associated with significantly lower rates of treatment failure, reduced risk of overall mortality, and a numerically reduced risk of adverse effects compared with ASPs. Our analysis was unique because the majority of included studies were contemporary, and we stratified our analyses according to average study-level severity of illness. Our findings: i) support a broader role for cefazolin in MSSA treatment, ii) refute the idea that ASPs should be used preferentially over cefazolin without qualification, and iii) indicate the need for robust comparative studies in the most critically ill patients affected by MSSA.

Although our analysis supports a broader role for cefazolin in clinical practice, there are concerns regarding the risk of treatment failure with cefazolin treatment. Overproduction of a type A beta-lactamase can occur in deep-seated, high-burden infections, efficiently hydrolyzing cefazolin [16,17]. While production of type A beta-lactamase may be a necessary condition for cefazolin failure in MSSA infection, the production of type A beta-lactamase does not appear sufficient to produce clinical failure in all cases. For example, the prevalence of type A beta-lactamase is highly variable. However, the role of any inoculum effect on clinical outcomes is poorly defined. Routine consultation of infectious diseases specialists, removal of infected catheters, early surgical intervention as indicated, and vigilant patient monitoring have all contributed to improved survival in MSSA BSI [45,46]. We observed similar beneficial effect sizes for cefazolin irrespective of high-burden source, which indicates that any clinical “inoculum effect” exerts a minimal influence on the majority of clinical outcomes. Additionally, our stratified analysis in both high and low severity of illness groups indicates that selection of an ASP is not necessarily a sur-

rogate for high underlying patient severity of illness. Our analyses support the clinical efficacy and tolerability of cefazolin when paired with other best practices.

Our finding that cefazolin appears more effective than ASPs is similar to previous investigations. In a 2014 meta-analysis, Vardakas et al. evaluated the comparative effectiveness and safety of ASPs vs. cephalosporins for the treatment of MSSA BSI [47], and found no difference in 90-day mortality risk in unadjusted (RR = 0.85, 95% CI: 0.54-1.32) or adjusted (RR = 1.42, 95% CI: 0.22-9.06) analyses. Unlike the present analysis, direct comparisons with cefazolin were not evaluated. More recently Li et al. systematically evaluated individual studies, finding no difference in clinical efficacy but improved tolerability with cefazolin [48]. Likewise, Loubet et al. found no significant difference in MSSA infection recurrence rates [49]. Four recent meta-analyses also support the tolerability and safety of cefazolin [50–53]. Lower mortality rates were reported with cefazolin in all three bacteremia studies [50,52,53]; however, Bidell et al. did not observe any differences in clinical failure (OR = 0.85, 95% CI: 0.41-1.76) [52]. While an emerging consensus regarding the benefits of cefazolin have been documented in these meta-analyses, none of the previous analyses have classified studies by average severity of illness, which could be a major confounder of treatment response and drug exposure. The present analysis provides additional evidence that cefazolin reduces the risk of treatment failure and mortality across multiple types of MSSA BSI and patient-populations, and highlights the need for additional studies in the most critically ill and vulnerable populations.

Our study has limitations. First, the majority of included studies were retrospective and carry inherent bias. However, to our knowledge, no randomized controlled studies comparing cefazolin and ASPs in MSSA BSI have been completed. Second, the definition of high-burden infection was generalized to include endovascular, bone and joint, pulmonary, and deep-abscess/tissue sources, but MSSA meningitis (n = 2; 0.15%) was rare. Concerns about the penetration of cefazolin into the blood-brain barrier frequently precluded consideration of its use in central nervous system infections. Additional prospective comparative studies are sorely needed in this population to validate these concerns. Nevertheless, other high-burden infections were common in our pooled analysis, representing 30.5% of the population. Infective endocarditis comprised 25.4% (n = 116/458) of cefazolin and 28.6% (n = 257/898) of ASP high-burden infections. Overall, our findings indicate that a majority of patients infected with MSSA may be safely treated with cefazolin if standard of care practices and infectious diseases consultation are utilized.

5. Conclusion

We found that cefazolin was associated with improved clinical outcomes and moderately lower risk of treatment-associated ADRs compared with ASPs in the treatment of MSSA BSI. Definitive prospective, randomized controlled trials are needed to establish the role of cefazolin and ASPs in serious, high-burden, MSSA infections affecting the most severely ill patients.

Declarations

Funding

No funding.

Competing Interests

Dr. Rhodes has received honoraria from ASHP (Bethesda MD) and research funds from the Center for Anti-Infective Research and Development (Hartford CT). The remaining authors have disclosed that they do not have any conflicts of interest.

Ethical Approval

Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.11.013.

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